A Comparison of Two Regimens of Topical Corticosteroids in the Treatment of Patients with Bullous Pemphigoid: A Multicenter Randomized Study

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Superpotent topical corticosteroids (CS) have been demonstrated to improve bullous pemphigoid (BP) patients' survival. We assessed whether a mild regimen using lower doses of topical CS and a shorter duration could improve the outcome of BP patients even more. Three-hundred and twelve BP patients were included in a multicenter randomized controlled trial and stratified depending on the extent of BP as moderate ($n=134$) or extensive ($n=178$). Patients were randomly assigned to the standard regimen (clobetasol propionate cream, 40 g per day initially, with CS tapering over 12 months) or the mild regimen (10–30 g per day), with CS tapering over 4 months. A noninferior rate of BP control was obtained with the mild regimen 156/159 (98%) as compared with the standard regimen 150/150 (100%; $P=0.005$). Event-free survival, that is, the combined outcome of deaths and life-threatening adverse events did not differ between the two treatment groups ($P=0.77$). However, upon adjusting through the Cox model for age and Karnofsky score, a strong beneficial effect of the mild regimen was observed in patients with moderate BP, with an almost twofold decrease in the risk of death or life-threatening adverse events relative to the standard regimen (hazard ratio = 0.54; 95% confidence interval, 0.30–0.97; $P=0.039$). This mild regimen allows a 70% reduction of the cumulative doses of CS and improves BP patients' outcome.

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Abbreviations: BP, bullous pemphigoid; CI, confidence interval; CS, corticosteroid

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INTRODUCTION

Bullous pemphigoid (BP) is the most frequent autoimmune blistering disease of the skin (Bernard *et al.*, 1995; Zillikens *et al.*, 1995; Gudi *et al.*, 2005; Baricault *et al.*, 2006; Langan *et al.*, 2008). BP mainly affects the elderly (Jung *et al.*, 1999), with mean age of patients between 77 and 81 years in recent studies (Joly *et al.*, 2002, 2005; Beissert *et al.*, 2007; Cordel *et al.*, 2007). The incidence rate of BP is about 200 cases per million per year among subjects over 75 years (Jung *et al.*, 1999; Gudi *et al.*, 2005). Importantly, a significant proportion of these elderly BP patients are in poor general condition, with a high prevalence of neurological and cardiovascular disorders (Roujeau *et al.*, 1998; Joly *et al.*, 2002, 2005; Rzany *et al.*, 2002; Cordel *et al.*, 2007). We recently demonstrated that old age and poor general condition are major deleterious prognostic factors of BP patients (Joly *et al.*, 2005).

Until recently, high doses of systemic corticosteroids (CS) were considered the standard treatment for BP patients (Fine, 1995). Following two large retrospective studies in France and Germany suggesting that such high doses of oral CS were poorly tolerated in these elderly patients and were associated with decreased survival (Roujeau *et al.*, 1998; Rzany *et al.*, 2002), a large controlled clinical trial demonstrated that high doses of superpotent topical CS increased survival of patients with extensive BP, as compared with oral prednisone, 1 mg kg^{-1} per day (Joly *et al.*, 2002). Moreover, topical CS

were demonstrated to be more effective than oral prednisone, as the rate of disease control obtained with topical treatment was 100 and 99% in patients with moderate and extensive BP, as compared with 95 and 91% with oral prednisone, respectively.

However, local and systemic complications were observed in patients treated with topical CS. Some of these adverse events may have been favored by the high doses of clobetasol propionate cream and the long duration of treatment (12 months). To improve the regimen of topical CS used to treat BP patients, we conducted a randomized trial comparing this 12-month regimen using high initial doses of topical CS, to a short-duration regimen of only 4 months, using lower initial doses of clobetasol propionate cream. The aim of this study was to assess whether this ''mild'' regimen of topical CS could improve survival, decrease the frequency of severe and life-threatening treatment side effects, while providing a noninferior rate of disease control relative to the ''standard'' regimen.

RESULTS

Patients

Between January 2002 and December 2004, 335 patients were assessed for eligibility. Informed consent could not be obtained from four patients or their family in fourteen patients with dementia. Previous use of medication effective against BP (in five patients), diagnosis of another autoimmune blistering skin disease (in three patients), and immediate withdrawal of consent (in one patient) were other reasons for exclusion. Of the remaining 312 patients, 134 had 10 or fewer new bullae daily (moderate disease) and 178 had more than 10 new bullae daily (extensive disease). Among the 134 patients with moderate disease, 69 were randomly assigned to receive the mild regimen and 65 the standard regimen of topical CS. Among the 178 patients with extensive disease, 90 were randomly assigned to receive the mild regimen and 88 to receive the standard regimen. Of the 159 patients assigned to receive the mild regimen, 8 patients received an initial daily dose of clobetasol propionate cream of 10 g, 64 patients received 20 g, and 87 received 30 g, based on their weight and extent of disease. Baseline characteristics of the patients are shown in Table 1. Among both patients with moderate BP and patients with extensive BP, the groups of patients assigned to receive the mild or the standard regimen of topical CS were well balanced in terms of number of daily new bullae (33.9 vs 32.3; $P=0.83$) and weight (68.3 vs 68.2 kg; $P=0.96$). However, patients assigned to receive the mild regimen were older than those receiving the standard regimen (83.3 vs 80.8 years; $P=0.02$) and had a somewhat lower Karnofsky score (60.8 vs 64.6%, $P=0.83$). Of the 312 patients, 3 included were lost to follow-up early after the initiation of treatment and were not available for the evaluation of efficacy by day 21 and were not included in the event-free survival analysis (Figure 1). The median duration of follow-up among surviving patients was 365 days (interquartile range: 363–365 days).

Disease control and survival

Among the 309 patients available for treatment efficacy by day 21, control of disease was achieved in all the 150 patients who were assigned to the standard regimen (100%; 95% confidence interval (CI), 98–100%) and in 156 of the 159 patients who were assigned to the mild regimen (68 of 69 patients with moderate BP and 88 of 90 with extensive BP; 98%; 95% CI, 95–100%; $P=0.005$) showing noninferiority of the mild regimen according to the prespecified 0.05 noninferiority range (Table 2).

A total of 118 patients died during the 1-year follow-up; 40 of these had moderate BP, and 78 had extensive BP. The causes of death were determined in 93 cases (79%); the main causes were deterioration of patients' general condition in 32 cases, sepsis in 29 patients (including 23 patients with pneumonia), cardiovascular diseases in 5 patients, and stroke in 6 patients.

Among the patients with moderate BP, 19 patients (28%) in the mild treatment group, and 21 (33%) in the standard treatment group died. Among the patients with extensive BP,

Table 1. Baseline characteristics of the patients

	Moderate disease (⩽10 new bullae per day)		Extensive disease (>10 new bullae per day)	
Characteristics of the patients	**Standard regimen (*n*=65)**	**Mild regimen (*n*=69)**	**Standard regimen (*n*=88)**	**Mild regimen (*n*=90)**
Age (years)	81.5 ± 8.4	84.8 ± 8.6	80.2 ± 12.2	82.2 ± 8.3
Sex (no)				
Male	28	25	37	39
Female	37	44	51	51
Karnofsky score (%)	68.3 ± 23.6	60.1 ± 22.4	61.9 ± 22.9	61.2 ± 22.1
Weight (kgs)	68.0 ± 14.1	65.9 ± 16.1	68.5 ± 16.4	70.0 ± 18.5
Number of new bullae daily	4.9 ± 10.3	6.0 ± 9.9	52.6 ± 91.5	55.2 ± 70.3

For all variables except sex, mean value ± SD is reported.

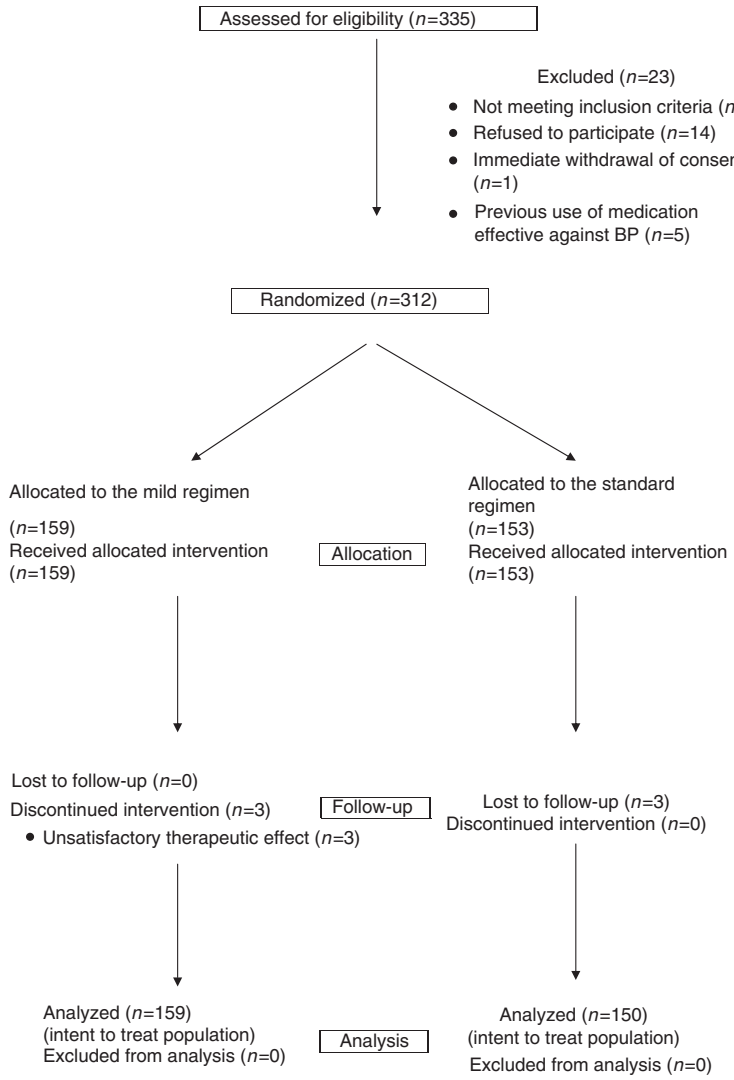

Figure 1. Flow chart of the study.

41 patients (45%) in the mild regimen group, and 37 patients (42%) in the standard regimen group died. The 1-year Kaplan–Meier overall survival rate was 62% (95% CI, 55–70%) in the group of patients treated with the mild regimen, and 61% (95% CI, 54–69%) in patients treated with the standard regimen ($P=0.77$, log-rank test). Forty-two life-threatening adverse events were observed in 33 patients. Comparison of Kaplan–Meier event-free survival curves taking into account both deaths and life-threatening adverse events did not reveal any difference between the two treatment groups ($P=0.95$; Figure 2a). After adjusting through the Cox regression model for the two major prognostic factors, age, and the Karnofsky score, a strong beneficial effect of the mild regimen was evidenced in patients with moderate disease with a hazard ratio of death of 0.52 (95% CI, 0.27–0.98; $P=0.044$) for patients treated with the mild regimen, and a hazard ratio of combined death or life-threatening side effect occurrence of 0.54 (95% CI, 0.30–0.97; $P=0.03$) for patients treated with the mild regimen, as compared with those treated with the standard regimen. In contrast, no effect of the treatment regimen on overall or event-free survival was evidenced in patients with extensive BP (hazard ratio = 1.18; 95% CI, 0.76–1.82; $P=0.46$ for overall survival).

Time to disease control and relapses

Mean time to achieve disease control was 7.9 ± 2.6 days in the 150 patients who were allocated to the standard regimen, and 8.2 ± 3.1 days in the 156 patients allocated to the mild regimen who experienced disease control ($P=0.56$; Table 2). A total of 52 out of the 150 patients in the standard treatment regimen group (35%; 95% CI, 27–43%) and 67 of the 156 patients in the mild regimen group (43%; 95% CI, 35–51%) experienced at least one relapse during the follow-up after median time of 149 and 140 days for the first relapse, respectively. Kaplan–Meier disease-free survival curves showed a higher rate of relapse in patients allocated to receive the mild regimen (especially after treatment withdrawal by day 120), as compared with patients allocated to receive the standard regimen (which lasted 12 months), with

Table 2. Main outcomes of the study depending on the extent of BP and treatment regimens

	Moderate disease ⩽10 new bullae per day		Extensive disease >10 new bullae per day	
	Mild regimen (*n*=69) Number of events (%)	Standard regimen (*n*=65) Number of events (%)	Mild regimen (*n*=90) Number of events (%)	Standard regimen (*n*=88) Number of events (%)
BP control by day 21	68 (99)	65 (100)	88 (98)	88 (100)
Time to achieve disease control (days)	7.7 ± 2.5[1]	7.8 ± 2.9[1]	8.6 ± 3.5[1]	7.9 ± 2.4[1]
Deaths	19 (28)	21 (32)	41 (45)	37 (42)
Severe side effects	67	97	127	130
Cumulative dose of clobetasol propionate (g)	435[2]	2,880[2]	879[2]	2,880[2]
Relapses	35 (51)	21 (32)	32 (36)	31 (35)

BP, bullous pemphigoid.
[1]Mean ± SD.
[2]Median.

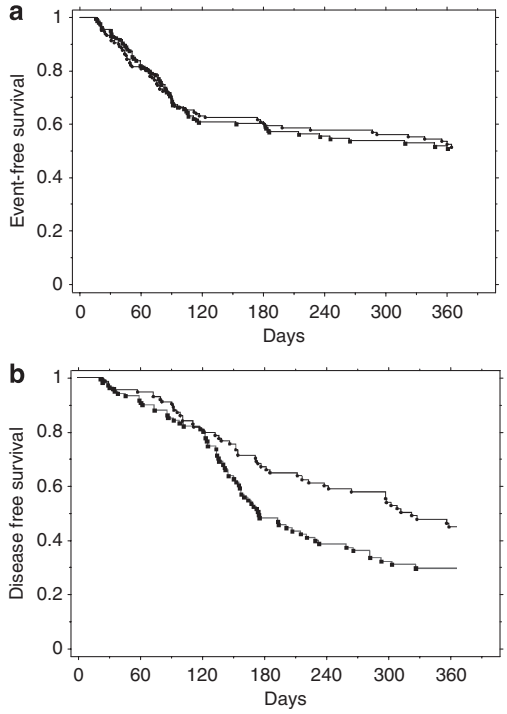

Figure 2. Event-free and disease-free survival curves of BP patients from the study. Kaplan–Meier estimates of event-free survival, i.e., combined outcome of death or life-threatening adverse event occurrence (**a**) and disease-free survival (**b**) of BP patients according to treatment regimen (■ patients treated with the mild regimen of topical corticosteroids; ● patients treated with the standard regimen).

1-year disease-free survival rates of 30 and 45%, respectively ($P=0.012$; Figure 2b).

Treatment adverse effects and cumulative doses of treatment

Overall, 421 severe side effects were reported in 178 patients, with 227 severe side effects reported in 89 patients from the standard regimen group (2.55 severe side effects per patient), and 194 in 89 patients from the mild regimen group (2.18 severe side effects per patient; $P=0.045$; Table 2). Main severe side effects in the standard and mild regimen groups were diabetes mellitus in 34 and 18 patients ($P=0.025$), cardiovascular and neurovascular disorders in 35 and 21 patients ($P=0.034$), and severe infections in 32 and 27 patients ($P=0.57$), respectively. Main cutaneous side effects were purpura, which was reported in 39 and 31%, severe skin atrophy in 10 and 8%, and striae in 3 and 2% of patients treated with the standard regimen and the mild regimen, respectively. The median cumulative dose of clobetasol propionate cream applied during the study (including additional treatment in relapsing patients) was 71% lower in the mild regimen group (825 g with range 75–2,880 g) than in the standard regimen group (2,880 g with range 600–6,960 g; $P<10^{-4}$).

Hypothalamo–pituitary–adrenal axis suppression testing

Hypothalamo–pituitary–adrenal axis suppression tests were performed in a subgroup of 28 BP patients recruited in one center who received a daily dose of clobetasol propionate of 20 g ($n=9$), 30 g ($n=9$), or 40 g ($n=10$). Plasma cortisol levels measured at day 0 were within the normal range (250–850 nmol l^{-1}) in all cases. A positive response to the administration of Cosyntropin was observed at day 0 in all but one case. A positive response to the Cosyntropin test was observed on days 7 and 30 in 5 of 18 (28%) and 4 of 16 (25%) patients treated with the mild regimen and in 1 of 8 (12%) and 2 of 10 (20%) patients treated with the standard regimen.

DISCUSSION

This study confirmed the extremely high efficacy of topical CS in the treatment of BP, as the rates of disease control obtained with the mild and standard regimens used in this study (98 and 100%, respectively) were almost identical to those obtained in our initial controlled trial, which tested the standard regimen (99% of control in extensive BP and 100% in moderate BP; Joly *et al.*, 2002). These findings confirm that superpotent topical CS are the most effective treatment for patients with BP, including those with an extensive disease, limiting at least initially the need for immunosuppressive drugs, which are poorly tolerated in these elderly patients (Krain *et al.*, 1972; Burton *et al.*, 1978; Thivolet *et al.*, 1985; Guillaume *et al.*, 1993; Paul *et al.*, 1994; Bohm *et al.*, 1997;

Grundmann-Kollmann *et al.*, 1999; Beissert *et al.*, 2007). It is likely that this extremely high efficacy of high potency topical CS is due to of both local and systemic effects, as demonstrated by the low number of positive response to the Cosyntropin test on day 7 or even on day 30 after epithelialization of skin lesions. However, high potency topical CS were more effective than oral CS in our previous study (Joly *et al.*, 2002) with fewer side effects, a difference that could hardly be explained by systemic effect alone. It is possible that the systemic absorption of topical CS may give prolonged, though potentially lower, systemic steroid levels.

Our results clearly demonstrate the efficacy of reduced initial daily doses of 10–30 g of clobetasol propionate adapted to the patient's weight and extent of disease. The disease was controlled by day 21 in 98% of patients treated with the mild regimen, a result nearly identical and significantly noninferior to that obtained with the standard regimen, whatever the extent of BP. Mean time to achieve disease control was short (about 8 days), with no difference between the two treatment groups. Importantly, the outcome of BP patients with moderate disease treated with the mild regimen was significantly improved, whereas this improvement was not apparent in unadjusted comparisons of overall or event-free survival over 1 year. It was revealed by comparisons adjusted for the two main prognostic factors of BP, age, and the Karnofsky score through the Cox model, with an almost twofold reduction in the risk of dying or experiencing a life-threatening side effect during the first year of treatment. This difference between adjusted and unadjusted comparisons is a consequence of the older age and poorer general condition of patients assigned to the mild regimen. Indeed, the mortality rate in subjects aged between 80 and 90 years in France is 6.5% per year. Moreover, the standardized mortality rate of BP patients in France and in Europe is between 20 and 30% per year, that is, between three and four times higher than that in the general population (Gudi *et al.*, 2005; Joly, 2008; Langan *et al.*, 2008). In view of these high mortality figures, the 2.5-year older average age of patients assigned in the mild regimen group (83.3 vs 80.3 years) should result in a markedly lower 1-year survival. Taken together, older age and poorer general condition of patients assigned to the mild treatment group may explain that the beneficial effect of the mild regimen of topical CS was only evidenced after adjusting for age and the Karnofsky score. This beneficial effect was not observed in patients with extensive BP probably because the initial doses of topical CS applied to patients with extensive BP assigned to the mild regimen group (20–30 g per day) were closer to those used in the standard regimen (40 g per day) than the doses of applied to patients with moderate BP (10–20 g per day).

The use of lower initial doses of clobetasol propionate cream, and a shorter treatment duration led to a 70% reduction in the cumulative doses of topical CS applied. Indeed, although the initial doses of patients with moderate or extensive BP assigned to the mild regimen were 20 and 30 g per day as compared with 40 g per day in patients assigned to the standard regimen, the treatment was stopped after only 4 months in patients assigned to the mild regimen, instead of a progressive decrease over 12 months in patients assigned to the standard regimen. Consistently, we observed a significant reduction of severe treatment side effects, especially those caused by the systemic absorption of topical CS, such as severe insulin-dependent diabetes mellitus, and cardiovascular disorders, favored by the applications of high doses of topical CS over a prolonged period. It is likely that the high rate of severe treatment side effects observed in this study is mainly because of (1) the very old age of many patients, (2) the inclusion of almost all consecutive cases of BP patients seen, (3) an excellent follow-up, and (4) a recruitment bias in this hospital-based series. Indeed, many BP patients in good general condition and/or with a limited disease are no longer referred to Dermatology Departments in France. Consequently, hospitalized BP patients are predominantly the older ones, and those with the poorest general condition and/or the most severe disease.

We observed a higher rate of relapse especially after treatment withdrawal by day 120 among patients treated with the mild regimen (43%) as compared with those treated with the standard regimen (35%) who continued to receive substantial doses of clobetasol propionate for 8 additional months. Interestingly, we observed a clear-cut separation of the two curves from months 4 to 6, with then a parallel evolution of the curves from months 6 to 12. It should be emphasized that although very few studies in the literature have reported the rate of relapse in BP patients, a significant proportion of them relapse despite long-term ongoing therapy with either topical or even oral CS (Joly *et al.*, 2002). Interestingly, the 35 and 43% rates of relapse observed in this study were close to the 46% rate of relapse observed among patients treated with 1 mg kg^{-1} per day of oral prednisone in our previous clinical trial (Joly *et al.*, 2002).

Overall, this study demonstrates that a mild regimen of topical CS is as effective as the standard regimen of high doses of topical CS for the treatment of patients with BP. The 70% reduction in the cumulative doses of CS led to a major decrease of the cost of treatment. Moreover, it resulted in fewer treatment side effects and yielded a twofold reduction of the risk of death or life-threatening treatment side effects among patients with moderate BP. The short duration of this mild regimen should improve the acceptability, as the consolidation phase during which CS doses are tapered lasts only 3 months. In our opinion, the major advantages of this mild regimen outweigh the slightly higher rate of relapses observed. Because these relapses were mainly observed after treatment withdrawal by month 4, we are currently evaluating the efficacy of weekly applications of topical CS vs low doses of methotrexate as maintenance therapy.

MATERIALS AND METHODS

Study patients

Twenty-three dermatologic centers in France participated in this prospective randomized study. The study was approved by the ethics committee of Upper Normandy and written informed consent was obtained from each patient. This trial was registered at www.clinicaltrials.gov (NCT 00213421) and made in accordance with the

Declaration of Helsinki Principles. Consecutive patients with newly diagnosed BP were eligible for entry if the following criteria were all met: clinical features suggestive of BP (Vaillant *et al.*, 1998; Joly *et al.*, 2004); subepidermal blister on skin biopsy (Courville *et al.*, 2000); and linear deposits of IgG and C3 along the basement membrane zone by direct immunofluorescence (Joly *et al.*, 1997). Exclusion criteria were predominant or exclusive mucosal involvement, treatment with oral or topical CS, dapsone, or immunosuppressive drugs during the previous 6 months.

Study design

This randomized study compared two parallel groups of patients treated with either a standard (Joly *et al.*, 2002) or mild regimen of topical CS. As the primary outcome was event-free survival, blinding was not deemed necessary. Randomization between the two regimens was stratified according to center and extent of disease categorized as moderate ($\leqslant$10 new bullae appearing daily on average during the previous 3 days) or extensive ($>$10 new bullae per day). Randomization was performed centrally with the use of random numbers in permuted blocks of four within each stratum. Patients were treated with topical applications of 0.005% clobetasol propionate cream (Dermoval cream; Glaxo SmithKline, Philadelphia, PA). The standard regimen consisted of an initial dose of 40 g per day, irrespective of the disease severity or patient weight. Clobetasol propionate cream (20 g) was applied twice daily on the entire body surface, until 15 days after disease control had been attained. The doses were then reduced to 20 g daily for 1 month, 10 g daily for 2 months, 10 g every other day for 4 months, and finally, 10 g twice a week for 4 months. Treatment was stopped after 12 months. Patients assigned to the mild regimen had their initial dose adapted to their weight and extent of BP. Namely, patients with extensive BP received a daily dose of 20 g of clobetasol propionate if their weight was less than 45 kg, or 30 g if it was at least 45 kg. This initial dose was applied until 15 days after disease control; thereafter, the doses were reduced to 20 or 30 g every other day for 1 month, 20–30 g twice a week for 1 month, and finally 20–30 g once a week for 1 month, respectively. Treatment was stopped after 4 months. Patients with moderate BP received a daily dose of 10 or 20 g daily depending on whether their weight was less or at least 45 kg. Fifteen days after disease control, the initial dose was reduced to, respectively, 10 or 20 g every other day for 1 month, twice a week for 1 month, and once a week for 1 month, before treatment withdrawal after 4 months.

Relapse was defined as the occurrence of at least three new bullae daily for 3 consecutive days during the period when CS doses were being reduced or after treatment withdrawal and/or the occurrence of urticarial lesions, which did not disappear spontaneously within 3 days. For patients who experienced a relapse during the dose reduction period, the dose was reincreased to the previous level. Patients who experienced a relapse after treatment withdrawal were treated using the following doses of clobetasol propionate cream: 10 g daily for patients with a localized relapse (that is, bullae in a single area); 20 g daily for patients with a moderate but nonlocalized relapse (that is, at most 10 new bullae per day in at least two separate areas); and 30 g daily for patients with extensive relapse (that is, more than 10 new bullae per day). Other therapy that might have affected BP activity was avoided throughout the study period.

Baseline and follow-up measurements

The Karnofsky score was assessed at baseline. This score is a measure of the patient's general condition and degree of autonomy on a scale ranging from 0 to 100, with higher scores indicating better condition and greater autonomy (Crooks *et al.*, 1991). The number of new bullae that appeared daily was recorded. Because of the high mortality reported in many recent studies during the first year after BP diagnosis, the follow-up was limited to 12 months. At each follow-up visit (on days 7, 14, 21, 30, 90, 120, 180, 270, and 360), patients underwent physical examination and the number of new bullae that appeared daily was noted, as was the number of units of clobetasol propionate cream that had been used. If applicable, the date of relapse was recorded, as were the date and cause of death. Any adverse events were precisely assessed on a standardized form, and their severity was graded 1 for mild effects, 2 for moderate effects, 3 for severe effects, or 4 for life-threatening effects, according to the standard criteria of the World Health Organization (WHO Collaborating Centre for International Drug Monitoring, 1992).

Test for adrenal suppression

Plasma cortisol levels were measured at 0800 hours and 2 hours after intravenous administration of 250 μg of 1–24 corticotropin (Cosyntropin test) in 28 BP patients recruited in one center who received a daily dose of clobetasol propionate cream of 20 g ($n=9$), 30 g ($n=9$), or 40 g ($n=10$). Hormone measurements were performed before treatment (day 0), after 7 days of treatment and after epithelialization of skin lesions on day 30. A positive response was defined as an increase of plasma cortisol level higher than 600 nmol l^{-1}, 60 minutes after the intravenous administration of 1–24 corticotropin.

Statistical analysis

The two primary end points were: (1) disease control at day 21, defined as the absence of new bullae for 3 consecutive days and (2) the combined outcome of death of any cause or life-threatening adverse events (that is, event-free survival) over the 1-year follow-up. In addition to the overall analysis, separate analyses were performed for patients with moderate and extensive BP. Secondary end points were: time to achieve disease control; occurrence of severe (grade 3 or 4) side effects (adverse events requiring hospitalization or prolongation of hospitalization or life-threatening events) during the follow-up year; occurrence of relapses during follow-up; and cumulative doses of clobetasol propionate cream used during the study period.

The study was designed to have 80% power to detect a 33% reduction in the 1-year rate of deaths or life-threatening events, from 40 to 27%, with the one-sided log-rank test and a type I error of 5%. To achieve this power, 157 patients were required in each treatment group. For disease control at day 21, this sample size yields greater than 95% power to detect noninferiority of the mild regimen with a noninferiority range of 0.05 relative to 0.99 disease control rate with the standard regimen for 0.99 expected control rate with the mild regimen. Similarly, it yeilds greater than 90% power to detect noninferiority of the mild regimen with a noninferiority range of 0.05 relative to 0.99 disease control rate with the standard regimen for 0.98 expected control rate with the standard regimen. Intention to treat analyses were performed. No interim efficacy analysis was either scheduled or performed. We checked that all the elements of

good reporting for noninferiority studies in the revised Consolidated Standards of Reporting Trials statement were fulfilled in this report.

Distributions of event-free, overall, and disease-free survivals according to treatment group were estimated by the Kaplan–Meier method and compared with the use of the log-rank test. Disease-free survival was defined as the time from randomization to the occurrence of the first relapse. A Cox model was used to adjust the comparisons of event-free survival between treatment groups for baseline characteristics that were previously demonstrated to have prognostic significance, namely older age (>83 vs $\leqslant 83$ years) and poor general condition as measured by the Karnofsky score (>40 vs $\leqslant 40$; Joly *et al.*, 2005). Exact binomial probabilities were used to estimate 95% CIs for the rates of disease control. Noninferiority of the mild regimen was tested with reference to 0.99 disease control rate with the standard regimen for a 0.05 noninferiority range (that is, down to 0.94 control rate) using a standard parametric test.

The Mann–Whitney test was used to compare times to achieve disease control, as well as cumulative doses of clobetasol propionate. For all tests, two-sided *P*-values less than 0.05 were considered to indicate statistical significance. Continuous variables are expressed as mean ± SD. Software packages SAS version 8.02 (SAS Institute, Cary, NC) and StatXact version 7 (Cytel Software Corporation, Cambridge, MA) were used.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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REFERENCES

Baricault S, Sparsa A, Courville P, Bravard P, Bedane C, Joly P (2006) Incidence of bullous pemphigoid in France. *Ann Dermatol Venereol* 133:4S1

Beissert S, Werfel T, Frieling U, Böhm M, Sticherling M, Stadler R *et al.* (2007) A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil in the treatment of bullous pemphigoid. *Arch Dermatol* 143:1536–42

Bernard P, Vaillant L, Labeille B, Bedane C, Arbeille B, Denoeux JP *et al.* (1995) Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. *Arch Dermatol* 131: 48–52

Bohm M, Beissert S, Schwarz T, Metze D, Luger T (1997) Bullous pemphigoid treated with mycophenolate mofetil. *Lancet* 349:541

Burton JL, Harman RR, Peachey RD, Warin RP (1978) Azathioprine plus prednisone in the treatment of pemphigoid. *BMJ* 2:1190–1

Cordel N, Chosidow O, Hellot MF, Delaporte E, Lok C, Vaillant L *et al.* (2007) Neurological disorders in patients with bullous pemphigoid. *Dermatology* 215:187–91

Crooks V, Waller S, Smith T, Hahn TJ (1991) The use of the Karnofsky performance scale in determining outcomes and risk in geriatric out patients. *J Gerontol* 46:M139–44

Courville P, Kupfer I, Gilbert D, Thomine E, Metayer J, Joly P (2000) Evaluation of histological criteria for bullous pemphigoid. Correlation with antigens recognized by immunoblotting of anti-epidermal autoantibodies. *Ann Pathol* 20:564–9

Fine JD (1995) Management of acquired bullous skin diseases. *N Engl J Med* 333:1475–84

Grundmann-Kollmann M, Korting HC, Behrens S, Kaskel P, Leiter U, Krähn G *et al.* (1999) Mycophenolate mofetil: a new therapeutic option in the treatment of blistering autoimmune diseases. *J Am Acad Dermatol* 40:957–60

Gudi VS, White MI, Cruickshank N, Herriot R, Edwards SL, Nimmo F *et al.* (2005) Annual incidence and mortality of bullous pemphigoid in the Grampian Region of North-East Scotland. *Br J Dermatol* 153:424–7

Guillaume JC, Vaillant L, Bernard P, Picard C, Prost C, Labeille B *et al.* (1993) Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. *Arch Dermatol* 129:49–53

WHO Collaborating Centre for International Drug Monitoring (1992) *International Monitoring of Adverse Reactions to Drugs: Adverse Reaction Terminology*. Uppsala, Sweden

Joly P (2008) Incidence of bullous pemphigoid and pemphigus is increasing in elderly people in the UK. *BMJ* 9:337

Joly P, Benichou J, Lok C, Hellot MF, Saiag P, Tancrede-Bohin E *et al.* (2005) Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol* 141:691–8

Joly P, Courville P, Lok C, Bernard P, Saiag P, Dreno B *et al.* (2004) Clinical criteria for the diagnosis of bullous pemphigoid: a reevaluation according to immunoblot analysis of patient sera. *Dermatology* 208:16–20

Joly P, Gilbert D, Thomine E, Delpech A, Courville P, Young P *et al.* (1997) Relationship between the *in vivo* localization and the immunoblotting pattern of anti-basement membrane zone antibodies in patients with bullous pemphigoid. *Arch Dermatol* 133:719–24

Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E *et al.* (2002) A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 346:321–7

Jung M, Kippes W, Messer G, Zillikens D, Rzany B (1999) Increased risk of bullous pemphigoid in male and very old patients: a population-based study on incidence. *J Am Acad Dermatol* 41:266–8

Krain LS, Landau JW, Newcomer VD (1972) Cyclophosphamide in the treatment of pemphigus vulgaris and bullous pemphigoid. *Arch Dermatol* 106:657–61

Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith JP, West J (2008) Bullous pemphigoid and pemphigus vulgaris-incidence and mortality in the UK: a population based cohort study. *BMJ* 337:a180

Paul MA, Jorizzo JL, Fleischer AB, White WL (1994) Low-dose methotrexate treatment in elderly patients with bullous pemphigoid. *J Am Acad Dermatol* 31:620–5

Rzany B, Partscht K, Jung M, Kippes W, Mecking D, Baima B *et al.* (2002) Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol* 138:903–8

Roujeau JC, Lok C, Bastuji-Garin S, Mhalla S, Enginger V, Bernard P (1998) High risk of death in elderly patients with extensive bullous pemphigoid. *Arch Dermatol* 134:465–9

Thivolet J, Barthelemy H, Rigot-Muller G, Bendelac A (1985) Effects of cyclosporin on bullous pemphigoid and pemphigus. *Lancet* 1:334–5

Vaillant L, Bernard P, Joly P, Prost C, Labeille B, Bedane C *et al.* (1998) Evaluation of clinical criteria for diagnosis of bullous pemphigoid. *Arch Dermatol* 134:1075–80

Zillikens D, Wever S, Roth A, Hashimoto T, Brocker EB (1995) Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 131:957–8